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Hepatic pseudo-anisotropy: a specific artifact in hepatic diffusion-weighted images obtained with respiratory triggering

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Abstract

Purpose: Hepatic pseudo-anisotropy is an artifact observed in hepatic diffusion-weighted imaging under respiratory triggering (RT-DWI). To determine the clinical significance of this phenomenon, hepatic RT-DW images were reviewed.

Methods: 105 MR examinations including RT-DWI were assessed. The patient group included 62 non-cirrhotic and 43 cirrhotic individuals. All images were evaluated by mutual agreement of two radiologists from the viewpoints of incidence of pseudo-anisotropy and correlation between pseudo-anisotropy and the quality of trace images. The ADC of normal hepatic parenchyma of non-cirrhotic livers were measured in both areas with and without pseudo-anisotropy.

Results: Pseudo-anisotropy was observed in 60% of non-cirrhotic (37/62) and 30% of cirrhotic (13/43) images. The difference between two groups was statistically significant ($p < 0.001$). The quality of trace images showed a tendency to worsen as pseudo-anisotropy became significant. However, the quality of trace images was generally satisfactory, with only two patients whose trace images were difficult to interpret due to pseudo-anisotropy. The areas with pseudo-anisotropy showed higher ADC than those without pseudo-anisotropy ($p < 0.001$).

Conclusion: Pseudo-anisotropy is a type of artifact that originates from respiratory movement. Even though respiratory triggering is employed, ADC measurement of the liver is inaccurate because of pseudo-anisotropy, especially in non-cirrhotic patients.

Keywords: diffusion-weighted image, liver, pseudo-anisotropy, respiratory motion

Introduction

Diffusion-weighted single-shot echo-planar imaging (DWI), whose main characteristic is high contrast resolution, is increasingly being adopted for a range of diseases (1-3). Notably, rapid generalization of parallel imaging techniques, represented by sensitivity encoding (SENSE) (4, 5, 6, 7), enables this sequence to be used for diagnosis of body malignancies (6-8). Many authors have reported the usefulness of DWI with simultaneous uses of SENSE in the diagnosis of various malignant tumors.

On the other hand, control of physiological motion is important to obtain reliable data in DWI when the principle of this sequence is taken into consideration (9). In particular, to acquire clinically useful hepatic DWI, careful concern for respiratory motion and cardiac pulsation is crucial. For obtaining fine DW images, long enough TR and multiple numbers of excitation (NEX) are the indispensable conditions because body DWI has very low signal-to-noise ratio. To cope with these two conditions, respiratory triggering is almost the only way, because the acquisition of DWI usually consists of four individual parts; T2-EPI without motion proving gradient (MPG) and three DWIs having three different MPG directions. The evocation of each part is sequentially performed on the same slices. Therefore, long enough intervals are necessary for T1-recovery between each part (10). This is the reason why DWI needs long TR. Of course, not only respiratory triggering but also cardiac gating should be used (11); however, simultaneous use of these two gating takes too much time for actual patients at current time. These are the reasons why multiple NEX is necessary for body DWI. With increased number of excitations, the probability of data acquisition during the diastolic phase would increase. Of course, this is not an ideal solution, but we currently believe that this method would be more practical than

simultaneous use of cardiac and respiratory triggering. Use of butyl scopolamine shortens the diastolic phase and worsens the image quality of DWI, even though the NEX is set to four or five (12). Accordingly, at this moment, we think that the optimal conditions for acquiring fine hepatic DW images are the simultaneous use of respiratory triggering, multiple NEX and no use of cardiac gating or butyl scopolamine.

In actual interpretation of hepatic DWI acquired with the abovementioned imaging options, however, we often encounter curious phenomena: more specifically, localized signal loss depending on difference of MPG direction is often observed in the hepatic parenchyma. Few of these are seen in other images with different MPG directions. At first glance, they look like anisotropy of the hepatic parenchyma, even though histological structures which can cause localized increases in diffusion are never present in the liver (Figure 1). This phenomenon is therefore assumed not to be real anisotropy but a kind of artifact. In this paper, we name this phenomenon 'hepatic pseudo-anisotropy' and assess its incidence and etiology.

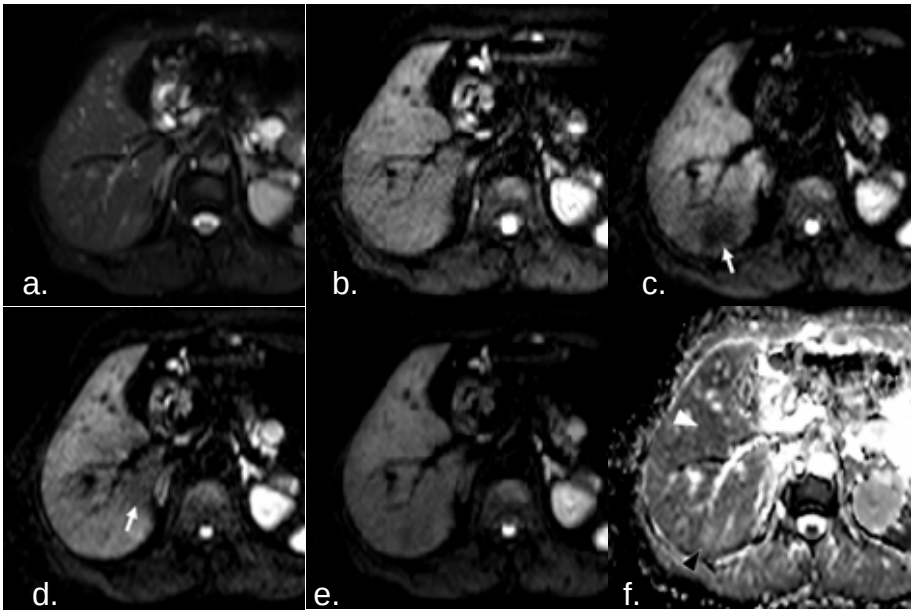

Figure 1

70 year old non-cirrhotic male with intrahepatic cholangiocellular carcinoma is shown (The hepatic tumor itself is not depicted on the figures). Ill-defined low signal areas were noted in DWI-Y (Figure 1c) and DWI-Z (Figure 1d), which were not observed in T2-EPI (Figure 1a) and DWI-X (Figure1b) (white arrows). These lesions were typical for hepatic pseudo-anisotropy. On trace images, these low-signal areas were not prominent because signal intensity of each pixel was averaged on trace image (Figure 1e). However, the area with pseudo-anisotropy was observed as a slightly higher-signal area on ADC map (Figure 1f, black arrowhead) and its ADC measured 2.23 x 10^{-3} mm^2/sec. The ADC of the hepatic parenchyma without pseudo-anisotropy measured 1.53 x 10^{-3} mm^2/sec (white arrowhead).

Methods

Patient group

MR examinations of the upper abdomen including DWI covering the whole liver were performed in 156 patients from July 2006 to August 2006 at National Cancer Center Hospital East. Among them, the 105 patients in whom the respiration triggering of each patient was considered to have succeeded, and who gave us approval to use the imaging data for scientific analysis, and did not have past history of hepatic resection, were adopted as candidates for this study. We reported our intended study to our ethics committee; however, the committee indicated that its approval was not required. At the time of MR examination, patients provided consent, which allowed use of their data for research purpose. The diagnostic radiologists who were in charge of each MR examination judged the success or failure of respiratory triggering of each patient.

The group comprised 66 males and 39 females, ranging from 21 to 85 years old (median 66 years). The details of the diagnoses are the following: 43 patients with hepatocellulcar carcinoma (HCC), 18 with pancreatic cancer, 13 with hepatic metastasis

due to colorectal cancer, ten normal cases, six with intraductal papillary mucinous neoplasm of the pancreas, three with intrahepatic cholangiocellular carcinoma, three with bile duct cancer, two with gastric cancer, two with adenomyomatosis of the gallbladder and one case each of solid and pseudopapillary tumor of the pancreas, hepatic hemangioma, focal nodular hyperplasia, hepatic abscess and drug-induced hepatitis. The above-mentioned diagnoses were pathologically confirmed in malignant diseases; however, the remaining benign diseases were diagnosed clinically by blood sample data and follow-up imaging examinations. All patients diagnosed with HCC had accompanying clinically diagnosed cirrhosis. However, the extent of cirrhosis in each patient was not always assessed by physicians. No other cirrhotic patients were noted in the remaining cases. The only preparation before the examination was an eight-hour fast. Existing daily drugs were not stopped before examination. No antispasmodic drugs were administered before DWI was obtained.

Imaging protocols

The MR apparatuses we used were a Gyroscan Intera Master 1.5T and a SENSE-body coil (Philips Medical, Best and Heeren, the Netherlands). These apparatuses and the sequences described below are all commercially available and were purchased from the manufacturer as Release 11.

Diffusion-weighted single-shot echoplanar imaging with simultaneous use of SENSE and respiration triggering was obtained (TR/TE = 800-3000/73, b-factor = 0, 500 sec/mm^2, SPIR (spectral presaturation with inversion recovery) for fat suppression, matrix size = 256 x 97, half scan factor = 0.693, reduction factor of SENSE = 2.0, FOV = 35 x 28 cm, number of excitations (NEX) = 5, slice thickness/gap = 7 mm/1 mm, 22 axial slices,

respiration trigger, actual scan time = 2–3 min). TR was customized in each patient to adjust to the length of the expiratory duration time. MPG pulses were placed along the three X (left to right), Y (anterior to posterior) and Z (cranial to caudal) -axes. Each image series, in which MPG pulses were placed along each direction, were respectively called DWI-X, DWI-Y and DWI-Z in this study. During image evaluation, we used DWI-X, DWI-Y, DWI-Z and trace images synthesized from DWI-X, DWI-Y and DWI-Z. The slice thickness, gap and FOV were occasionally changed, depending on the size of the liver in each patient, to cover the whole liver. No cardiac gating was employed.

Image analysis

In this study, only the right hepatic lobes were evaluated, since cardiac gating was not employed (10. 12). Presence or absence of pseudo-anisotropy and its grade in each patient were visually evaluated by mutual agreement of two diagnostic radiologists (K.N. and Y.K.). The evaluation details are listed below.

(i) The right hepatic lobe was roughly divided into four with the confluence of the anterior and posterior branch of the portal vein as the center (Figure 2). The quadrants were named the superior ventral area (SV), superior dorsal area (SD), inferior ventral area (IV) and inferior dorsal area (ID).

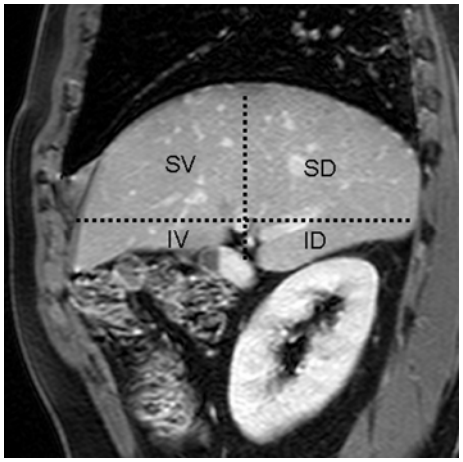

Figure 2

Division of right hepatic lobe for PA index evaluation is shown. With the confluence of the anterior and posterior branch of the portal vein as the center, the each quadrant is named the superior ventral area (SV), superior dorsal area (SD), inferior ventral area (IV) and inferior dorsal area (ID).

(ii) Two diagnostic radiologists interpreted DWI-X, DWI-Y and DWI-Z and judged the presence or absence of pseudo-anisotropy of each area in each series of DWI. If any one slice had signal loss that was assumed to be due to pseudo-anisotropy, which might have a negative influence on image interpretation, that DWI series was judged to be pseudo-anisotropy positive. One pseudo-anisotropy index (PA index) point was given for each area with pseudo-anisotropy of each series of DWI. Accordingly, each series of DWI was awarded zero to four points, so each patient would get zero to 12 points.

(iii) Only those patients whose PA indexes were zero were judged as pseudo-anisotropy negative. Other patients whose PA indexes were between one and 12 were judged as pseudo-anisotropy positive. The incidence of pseudo-anisotropy was calculated according to these criteria.

(iv) Separately from the results of interpretation of DWI-X, DWI-Y and DWI-Z, the image quality of trace images was graded into three by the same radiologists.

Grade 1: Pseudo-anisotropy was absent or only slightly present. The readers did not experience any difficulty in interpreting the images.

Grade 2: Pseudo-anisotropy was obvious; however, the readers were able to perform image interpretation.

Grade 3: Pseudo-anisotropy was prominent; hence, the readers felt difficulty in image interpretation.

Both the overall incidence of pseudo-anisotropy and individual incidences in DWI-X, DWI-Y and DWI-Z were calculated. The difference in pseudo-anisotropy incidence among each DWI series was tested for significance using the McNemar test. The differences in PA index among each DWI series were assessed using Wilcoxon's

paired signed rank test. A comparison of the incidence of pseudo-anisotropy between the patients with HCC and the remainder was made using the chi-squared test. In patients who were judged as pseudo-anisotropy positive, the correlation between the grade of the trace image grade and PA index was examined by Mann-Whitney U test..

ADC measurement in normal hepatic parenchyma was performed only in the non-cirrhotic patients with pseudo-anisotropy. The reason why cirrhotic patients were excluded from this procedure was to avoid the influence of cirrhotic change from ADC measurement. ADC maps were made in each patient using the two-point method (13). Two regions of interest (ROIs) were created in each patient; one in the area with pseudo-anisotropy and another in the area without. ROIs were placed on trace image and copied/pasted on ADC map using copy to temp/copy from temp function of MR apparatus. The reason why this method was selected was that pseudo-anisotropy was often unclear on ADC map as comparison with DWI. Intrahepatic structures, including lesions, were carefully excluded from the ROIs. These procedures were done under mutual agreement of two radiologists previously mentioned. The difference in ADCs with and without pseudo-anisotropy in each patient was compared using the paired t test.

The Stat Mate III package for Windows was used to carry out the abovementioned analyses.

Results

The overall incidence of pseudo-anisotropy was 48 % (50/105), and mean PA index was 2.99±2.98. When DWI-X, DWI-Y and DWI-Z were evaluated separately, the

incidence of each DWI series was 40% (42/105), 36% (39/105) and 41% (44/105), and PA indexes were 1.02±1.22, 0.70±1.02 and 0.98±1.09 respectively. The incidence of pseudo-anisotropy in each DWI series did not show any overt statistical difference (p = 0.34 in DWI-X vs. DWI-Y, p = 0.18 in DWI-X vs. DWI-Z, and p = 0.77 in DWI-Y vs. DWI-Z). The difference in PA index between DWI- X and DWI-Y showed statistically significant (p = 0.01), however there were no statistically significant differences between other pairs (p = 0.68 in DWI-X vs. DWI-Z, and p = 0.50 in DWI-Y vs. DWI-Z) (Table 1).

	DWI-X	DWI-Y	DWI-Z	Trace image
Incidence of pseudo-anisotropy*	40%(42/105)	37%(39/105)	42%(44/105)	48%(50/105)
PA index	1.02±1.22	0.70±1.02	0.98±1.09	2.99±2.98

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*No significant difference in each pair about incidence of pseudo-anisotropy
**P=0.011, ***P=0.50, ****P=0.68

Table 1. Incidence of pseudo-anisotropy and PA indexes in each DWI

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Pseudo-anisotropy was observed in 48%. The incidence in each DWI series did not show statistically significant difference. PA index in DWI-Y is significantly lower than that in DWI-X (P=0.11). However, no statistical difference of PA index can be pointed out between DWI-X and DWI-Z and between DWI-Y and DWI-Z.

In cirrhotic patients, the incidence of pseudo-anisotropy was 30 % (13/43). On the other hand, 60 % of the remaining patients showed pseudo-anisotropy (37/62). Statistical analysis revealed that the difference between these two was significant (p < 0.001) (Table 2).

	Cirrhotic patients	Non-cirrhotic patients
Incidence of pseudo-anisotropy	30%(13/43)	60%(37/62)

P<0.001

Table 2. Comparison of pseudo-anisotropy incidence between cirrhotic and non-cirrhotic patients.

The incidence of pseudo-anisotropy is significantly lower in cirrhotic patients than non-cirrhotic patients.

Concerning the quality of the trace images in the 50 patients who were pseudo-anisotropy positive, 29 grade 1 patients, 19 grade 2 patients, and only two grade 3 patients were noted. Statistical analysis was performed between the patient groups classified into grade 1 and combined patient group classified into grade 2 and grade 3. The reason why this statistical procedure was selected was that only two patients were classified into grade 3. The analysis showed that there was statistically significant correlation between the PA index points and the grades of visual evaluation. The patients with higher PA index showed a significant tendency to be classified into groups with higher grades ($p < 0.001$) (Figure 3).

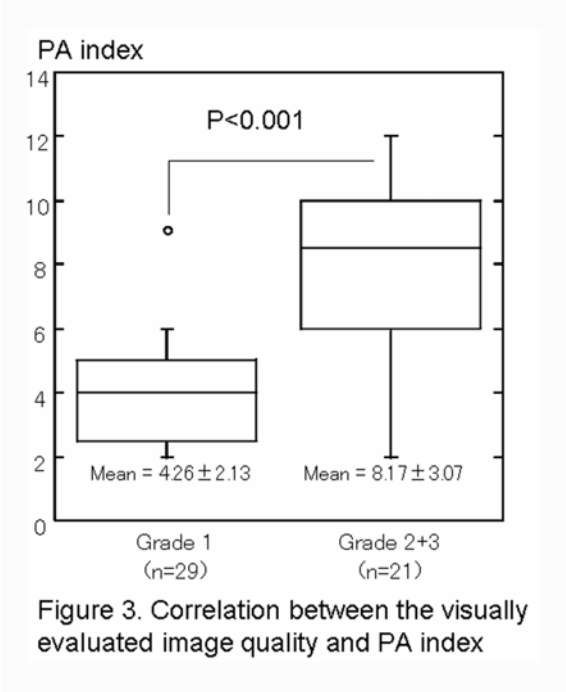

Figure 3. Correlation between the visually evaluated image quality and PA index

Figure 3. Correlation between the visually evaluated image quality of trace image and PA index in PA positive non-cirrhotic patients. The statistical examination revealed statistically significant correlation between the image quality grade and PA index points.

Mean ADC in areas with pseudo-anisotropy was 2.41±0.44 x10^{-3} mm^2/sec and that in areas without pseudo-anisotropy was 1.54±0.16x10^{-3} mm^2/sec. The difference between these was statistically significant ($p < 0.001$). The scattering of ADC was far smaller in areas without pseudo-anisotropy than in those with pseudo-anisotropy (Figure 4).

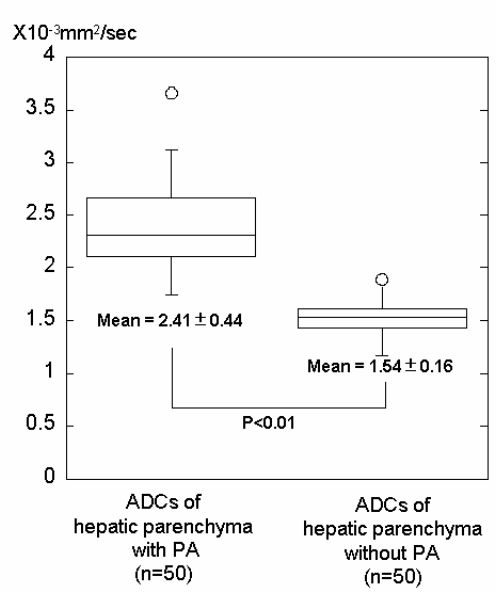

Figure 3. Difference of ADCs of hepatic parenchyma between with and without pseudo-anisotropy.

The difference of ADCs in hepatic parenchyma between with and without pseudo-anisotropy is shown. The ADCs in the hepatic parenchyma with pseudo-anisotropy is significantly higher than those without pseudo-anisotropy (P < 0.01). The data scattering is also larger in ADCs in the hepatic parenchyma with pseudo-anisotropy than those without pseudo-anisotropy.

Discussion

The high sensitivity to body malignancies of DWI has become a subject of interest on the part of many radiologists. The correct reason that DWI can visualize body malignancies hyperintensely has not yet been established; however, the high cellularity in tumors is assumed to be the main reason (14, 15). The water molecules in the extracellular fluid of cancer tissue may be more restricted in their Brownian motion than those in the surrounding normal tissue. Therefore, the mechanism of visualization of body malignancies is assumed to be basically the same as that of fresh brain infarctions (16).

Taking the abovementioned matters into consideration, correct compensation for physiological motion must be simultaneously used when this sequence is indicated in hepatic disease diagnosis (10-12). Hence, body DWI during free breathing and multiple NEX proposed by Takahara and his colleagues surprised us (17). In this method, the obtained images had sufficient image quality for interpretation even though no compensation had been simultaneously used for physiological movement. On reflection, though, this result appeared less miraculous. If all the water molecules in one voxel experienced the same motion-driven displacement, they would not theoretically show any change in signals on DW images, or in ADC measurement (18). Therefore, respiratory hepatic movement resembling uniform motion should not exert a large influence on the DW signal itself. However, actual DW images obtained using this method, were strongly influenced by respiratory hepatic movement. The hepatic lesions on the DW images obtained during free breathing show lower contrast to the surrounding hepatic parenchyma than the same lesions in DW images obtained with respiratory triggering,

since the signal of each hepatic lesion is a mixture of the real lesion signal and the surrounding structures on reconstructed DW images obtained during free breathing (11, 19). Moreover, for correct measurement in the left hepatic lobe, both respiratory and precise cardiac compensation are crucial (10, 12).

This study revealed that our DWI sequence, in which respiratory triggering was employed, did not have sufficient quality to measure the correct diffusion. A healthy liver is elastic and is easily distorted by slight external forces such as respiratory movement (20). Probably, the liver does not remain still, even at the end of the expiratory phase, and may show localized movement such as expansion, contraction and rotation. These motions are far smaller than respiratory movement; however, they may strongly influence the DWI signals, since they possess acceleration. In addition, these small motions are assumed to have direction because all the movements of an elastic body can be expressed as tensors (21). These hypotheses effectively explain the phenomena actually observed in hepatic DWI. Pseudo-anisotropy resembled localized accentuation of diffusion and was not usually observed in other DWI series with different MPG directions.

This study also presents some data which supports the hypotheses mentioned above. The incidence of pseudo-anisotropy was significantly lower in patients with HCC than in the remainder. All the patients with HCC in this study had clinically diagnosed accompanying cirrhosis. Disappointingly, the grade of cirrhosis in each patient had not always been assessed by physicians; therefore, a correlation between the grade of cirrhosis and the incidence of pseudo-anisotropy could not be determined in this study. However, this finding suggests that the incidence of pseudo-anisotropy decreases as livers became more rigid, and the flexibility of the normal liver was the one of the causes

of pseudo-anisotropy.

The results of this study include several pointers on how to increase the effectiveness of hepatic DWI in clinical scenarios. The main aim of hepatic DWI is to detect hepatic malignancies. In particular, it has already been proven that hepatic resection with the aim of total removal of tumor tissue improves the prognosis for metastatic liver disease deriving from colorectal cancer (22). Surgeons are therefore increasingly demanding accurate information from diagnostic radiologists that will enable them to determine the exact number and location of liver metastases as far as they can be found during operations. Radiologists are thus coming to acknowledge hepatic DWI as a useful screening method for hepatic metastases. However, in patients in whom hepatic pseudo-anisotropy due to respiratory movement is significant, the sensitivity to hepatic metastasis may decrease and thus not satisfy clinical demand if DWI is obtained under respiratory triggering. Due to current technical limitations, we believe that the imaging conditions employed in this study were not ideal but realistic for obtaining fine DW imaging of the whole liver; however, we need to investigate the possibility of hepatic DWI under breath-holding to suppress hepatic pseudo-anisotropy and stabilize the image quality.

Our study also revealed that most hepatic pseudo-anisotropy might not disturb the clinical image interpretation if the trace images were visually evaluated. There were only two patients whose trace image qualities were classified as grade 3. Conventional methods of hepatic DWI acquisition provided enough information in most patients even though pseudo-anisotropy occurred in many. These findings can be explained by the following reasons: the pseudo-anisotropy observed in one series of DWI with one MPG direction was not usually observed in the other series of DWI with different MPG

directions. Therefore, signal drop due to pseudo-anisotropy became less prominent in trace images because the signal intensities of each pixel in each DWI series were averaged on the trace images. However, this study also revealed that areas with pseudo-anisotropy showed a higher ADC than areas without it. Accordingly, ADC measurements in the liver are assumed to not be precise in many cases where hepatic DWI is acquired under respiratory triggering.

This study had several limitations. The chief issue is the validity of our methods of evaluation of pseudo-anisotropy. We visually assessed the range and incidence of pseudo-anisotropy; however, the strength of each artifact was not investigated at all. Therefore, PA index of each patient did not directly reflect the image quality or incorrectness of ADC measurement. From this view-point, our methods for evaluation were practical but not qualitative. Additionally, to prove our assumptions, we would need to perform a comparison between DWIs under respiratory triggering and under breath-holding. If our presumption is true, pseudo-anisotropy should disappear when the images are obtained under breath-holding. However, image acquisition under breath-holding was not performed in any cases in this study since the evaluated images were all retrospectively reviewed.

In conclusion, hepatic pseudo-anisotropy is an artifact specifically observed in DW images obtained under respiration. When the images were evaluated in detail, pseudo-anisotropy was observed in more than half of non-cirrhotic patients. The incidence of pseudo-anisotropy was less frequent in cirrhotic patients. This artifact was assumed to have originated in localized hepatic movement such as extension, contraction and rotation. In most patients, hepatic pseudo-anisotropy itself did not interfere with image interpretation; however, this artifact might increase the number of errors in ADC

measurements of the liver.

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